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PCT

NOTIFICATION D'ELECTION

(règle 61.2 du PCT)

Destinataire:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

en sa qualité d'office élu

Date d'expédition (jour/mois/année) 09 novembre 1998 (09.11.98)	
Demande internationale no PCT/FR98/00772	**Référence du dossier du déposant ou du mandataire** MD/B05B2628
Date du dépôt international (jour/mois/année) 16 avril 1998 (16.04.98)	**Date de priorité** (jour/mois/année) 16 avril 1997 (16.04.97)
Déposant ELAISSARI, Abdelhamid etc	

1. L'office désigné est avisé de son élection qui a été faite:

[X] dans la demande d'examen préliminaire international présentée à l'administration chargée de l'examen préliminaire international le:

19 octobre 1998 (19.10.98)

[ ] dans une déclaration visant une élection ultérieure déposée auprès du Bureau international le:

2. L'élection [X] a été faite

[ ] n'a pas été faite

avant l'expiration d'un délai de 19 mois à compter de la date de priorité ou, lorsque la règle 32 s'applique, dans le délai visé à la règle 32.2b).

Bureau international de l'OMPI
34, chemin des Colombettes
1211 Genève 20, Suisse

no de télécopieur: (41-22) 740.14.35

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Translation

PATENT COOPERATION TREATY 09/403085 10 T

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MD/MK/B 05 B 2628 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR98/00772	International filing date (*day/month/year*) 16 April 1998 (16.04.1998)	Priority date (*day/month/year*) 16 April 1997 (16.04.1997)
International Patent Classification (IPC) or national classification and IPC G01N 33/545		
Applicant BIO MERIEUX		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 October 1998 (19.10.1998)	08 July 1999 (08.07.1999)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR98/00772

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 4-15, as originally filed,
pages _____, filed with the demand,
pages 1, 1A, 2, 3, filed with the letter of 09 June 1999 (09.06.1999),
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-32, filed with the letter of 09 June 1999 (09.06.1999),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/3-3/3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-32	YES
	Claims		NO
Inventive step (IS)	Claims	1-32	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-32	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: EP-A-0 516 198
D2: US-A-4 246 350
D3: KEMPE M. ET AL.: "An Approach to Surface Imprinting Using The Enzyme Ribonuclease A" JOURNAL OF MOLECULAR RECOGNITION, Vol.8, 1995, pages 35 to 39.

1. Document D1, which is considered to represent the prior art closest to the subject matter of Claim 1, discloses the use of magnetic particles in a capture-detection method, as a capture (examples 2 and 5) or detection (Claim 6) phase as described in the preamble of Claim 1. These particles (pp.2-4) consist of a polymer which has coordination sites and is coprecipitated with a transition metal in order to form magnetic particles. An extra-particulate ligand (for example SPDP) enables a biological entity to be bonded to functional groupings (for example amine) of the polymer.

The subject matter of Claim 1 therefore differs from this known method in that the biological entity is

bonded to the transition metal.

The subject matter of Claim 1 is therefore novel (PCT Article 33(2)).

The problem to be solved by the present invention can therefore be considered to be that of providing another means of immobilizing a biological entity on particles containing a transition metal which are used in a capture-detection method.

The solution to this problem proposed in Claim 1 of the present application is considered to involve an inventive step (PCT Article 33(3)) for the following reasons:

Although the immobilization of a biological entity on polymer particles (by coordinate bonding) by means of a transition metal, itself bonded by coordination to a complex-forming grouping or chelator site of the polymer is known (cf. D2, col.1, lines 28 to 38 and D3, Fig.1), a person skilled in the art would not have found in these documents or the others representing the known prior art any indication encouraging the use of the particles resulting from such an immobilization in a method for capturing and detecting a target biological material. The reversible nature of the bond (the fixed protein can easily be detached or eluted from the particle, cf. D2, col.2, lines 1 to 3, and D3, abstract and Fig.2) would rather have been considered a shortcoming for this novel application.

Claims 2 to 29 depend on Claim 1 and therefore also

satisfy *per se* the requirements of the PCT as regards novelty and inventive step.

2. Claims 30, 31 and 32 relate to the use of a polymer as a capture and/or detection phase as implied in Claims 1, 2 and 3. The subject matter of these claims can be considered novel and to involve an inventive step for the same reasons as put forward in 1). above (PCT Article 33(2) and (3)).

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Abdelhamid ELAISSARI, David DURACHER, Christian PICHOT, Francois MALLET and Armelle NOVELLI-ROUSSEAU

Attn: PCT Branch

Application No. U.S. National Stage of PCT/FR98/00772

Filed: October 15, 1999 Docket No.: 104560

For: PROCESS FOR ISOLATING A TARGET BIOLOGICAL MATERIAL, CAPTURE PHASE, DETECTION PHASE AND REAGENT

TRANSLATION OF THE ANNEXES TO THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Attached hereto is a translation of the annexes to the International Preliminary Examination Report (Form PCT/IPEA/409). The attached translated material replaces pages 1-3 and the claims.

Respectfully submitted,

William P. Berridge
Registration No. 30,024

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. :

U.S. National Serial No. :

Filed :

PCT International Application No. : PCT/FR98/00772

VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below;

That I am knowledgeable in the French language in which the below identified international application was filed, and that, to the best of my knowledge and belief, the English translation of the amended sheets of the international application No. PCT/FR98/00772 is a true and complete translation of the amended sheets of the above identified international application as filed.

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application issued thereon.

Date: 22 September 1999

Full name of the translator : Norval O'CONNOR
For and on behalf of RWS Group plc

Post Office Address : Europa House, Marsham Way,
Gerrards Cross, Buckinghamshire,
England.

Process for isolating a target biological material, capture phase, detection phase and reagent

The present invention relates to the isolation or detection of a biological material, referred to as the target biological material, contained in a sample, by means of a process using a capture phase, and optionally a detection phase, according to which said material is exposed to the capture phase at least, and the capture phase/target biological material complex formed is then detected, optionally with said detection phase.

In the presentation of the invention which follows, reference is made in particular to the isolation of a target protein biological material, but, needless to say, the scope of the invention should not be limited thereto.

Thus, according to the invention, the expression "biological material" means, in particular, a protein or glycoprotein material such as an antigen, a hapten, an antibody, a protein, a peptide, an enzyme or a substrate, and fragments thereof; but also a nucleic material such as a nucleic acid (DNA or RNA), a nucleic acid fragment, a probe or a primer; a hormone.

According to EP-A-0,516,198, a process is described for detecting a biological material using a capture phase consisting of magnetic particles. This capture phase is obtained by co-precipitation of a transition metal and of a polymer which have available coordination sites to which the atoms of said metal come to bind, followed by binding of a biological species to reactive sites of said polymer via a bifunctional agent, said species having an affinity for the material to be detected.

In accordance with the article by M. Kempe et al. (1), a process is known for capturing a target protein which contains polyhistidine sequences, namely RNase A, according to which the high affinity of the imidazole group of histidine for metals is used.

This process comprises the following steps:

- a capture phase is used consisting of silica particles functionalized with methacrylate groups,

- a target protein and a metal-complexing agent, namely N-(4-vinyl)benzyliminodiacetic acid (VBIDA), are placed in contact with a metal, in order to obtain a complex resulting from coordination bonding between the metal and the imidazole groups of the histidine, and coordination bonding between the metal and the carboxyl groups of VBIDA, and

- said functionalized silica particles are placed in contact with the complex formed above.

This immobilization process does not lead to optimum binding of the target protein.

Document US-A-4,246,350 described a process for immobilizing an enzyme using a capture phase which consists of a macroporous polymer containing complexing groups linked to a transition metal. The drawback of such a capture phase results directly from the macroporous nature of the polymer. The reason for this is that, although this macroporous nature makes it possible to maximize the adsorption of the enzyme onto the capture phase, it becomes disadvantageous at the time of isolation of the enzyme using a detection phase, since the proportion of enzyme adsorbed in the polymer pores will not be accessible to said detection phase.

According to the present invention, a process is provided for isolating a target biological material, using a capture phase such that it makes it possible to optimize the binding of this material on this phase, while at the same time reducing, or even eliminating, any side reaction of adsorption of said material onto said capture phase. The interaction between the capture phase and the biological material is specific, thus making it possible, during isolation, to detect the proportion of biological material effectively bound to the capture phase.

For this purpose, the process for isolating a target biological material uses a capture phase which has the following properties:

it is in microparticulate form or in linear form, it consists of at least one first particulate or linear polymer, of hydrophilic apparent nature, and first complexing groups, linked covalently,

the first complexing groups are linked by coordination to a first transition metal,

the first transition metal is itself linked by chelation to a first biological species which is capable of specifically recognizing the target biological material.

According to one variant of the process of the invention, the capture phase defined above comprises a marker, in order to obtain a detection phase.

According to another variant of the process, a detection phase is also used which has the following properties:

it in microparticulate or linear form,

it consists of at least one second particulate or linear polymer, of hydrophilic apparent nature, and second complexing groups,

the second complexing groups are linked by coordination to a second transition metal,

the second transition metal is itself linked by chelation to a second biological species capable of specifically recognizing the target biological material,

it comprises a marker.

According to the invention, the term "microparticulate" means in the form of particles not more than 10 Πm in size. Preferably, they do not exceed 5 Πm in size.

The first and/or second particulate or linear polymer is advantageously a hydrophilic polymer, and in particular a functionalized polymer obtained by

CLAIMS

1. Process for isolating a target biological material contained in a sample, according to which a capture phase is provided, said target biological material is placed in contact with at least the capture material, and the capture phase/target biological material complex is detected,

said process being characterized in that,

the capture phase is in microparticulate or linear form and consists of at least one first particulate or linear polymer, with a hydrophilic apparent nature and first complexing groups, these groups being linked covalently to said first polymer and by coordination by a first transition metal, which is itself linked by chelation to a first biological species capable of specifically recognizing the target biological material.

2. Process according to Claim 1, characterized in that the capture phase comprises a marker in order to obtain a phase for detecting said biological material.

3. Process according to Claim 1, characterized in that a detection phase is also provided, which is in microparticulate or linear form and consists of at least one second particulate or linear polymer, of hydrophilic apparent nature, and second complexing groups, these groups being linked by coordination to a second transition metal, which is itself linked to a second biological species capable of specifically recognizing the target biological material, and a marker.

4. Process according to Claim 1, characterized in that the first polymer is chosen from the group of hydrophilic polymers.

5. Process according to Claim 3 or according to the combination of Claims 4 and 3, characterized in that the second polymer is chosen from the group of hydrophilic polymers.

6. Process according to Claim 4, characterized in that the first polymer is a functionalized polymer obtained by polymerization of a water-soluble monomer, of acrylamide, of an acrylamide derivative, of methacrylamide or of a methacrylamide derivative, of at least one crosslinking agent and of at least one functional monomer.

7. Process according to Claim 5, and optionally Claim 6, characterized in that the second polymer is a functionalized polymer obtained by polymerization of a water-soluble monomer, of acrylamide, of an acrylamide derivative, of methacrylamide or of a methacrylamide derivative, of at least one crosslinking agent and of at least one functional monomer.

8. Process according to Claim 6 and/or 7, characterized in that the water-soluble monomer is chosen from N-isopropylacrylamide, N-ethylmethacrylamide, N-n-propylacrylamide, N-n-propylmethacrylamide, N-n-isopropylmethacrylamide, N-cyclopropylacrylamide, N,N-diethylacrylamide, N-methyl-N-isopropylacrylamide and N-methyl-N-n-propylacrylamide, the monomer preferably being N-isopropylacrylamide (NIPAM).

9. Process according to Claim 6 and/or 7, characterized in that the functional monomer corresponds to formula I below:

$$CH_2=C(Z)-(X)_m-(R)_p-(Y)_n \quad (I)$$

Z represents H, a C1-C5 alkyl radical or a benzyl, -COOH or $-CO-NH-CH(CH_3)_2$ radical,

Y represents $-CH_2-COOH$, $-N(CH_2-COOH)_2$, $-N(CH-COOH)(CH_2-COOH)$, or $-N(CH_2-CH_2-NH_2)_2$

$$|$$
$$(CH_2-COOH)$$

X represents $-NH(CH_2-CH_2-)$, $--N(CH_2-CH_2-)_2$, $-N(CH_2-COOH)(CH_2-CH_2-)$, or $CH(COOH)-$,

R represents a linear hydrocarbon-based chain, optionally interrupted with at least one hetero atom such as O or N,

m and p are each an integer which, independently of each other, are equal to 0 or 1, and

n is an integer ranging between 1 and 3.

10. Process according to Claim 9, characterized in that the functional monomer is chosen from carboxylic derivatives, optionally containing nitrogen, itaconic acid, acrylic derivatives and methacrylic derivatives.

11. Process according to any one of Claims 1 to 10, characterized in that the capture phase is in microparticulate form and in that the average particle size is not more than 5 µm.

12. Process according to any one of Claims 3 and 5 to 11, characterized in that the detection phase is in microparticulate form and in that the average particle size is not more than 5 µm.

13. Process according to Claim 1, characterized in that the capture phase also comprises a flat or particulate support.

14. Process according to Claim 13, characterized in that the support is particulate and consists of an organic or inorganic, hydrophilic or hydrophobic core.

15. Process according to Claim 14, characterized in that said core is chosen from the group comprising polystyrene, silica and metal oxides.

16. Process according to Claim 14 or 15, characterized in that said core also contains a magnetic compound.

17. Process according to any one of Claims 14 to 16, characterized in that said core is coated with said first polymer, the latter being linear.

18. Process according to any one of Claims 14 to 16, characterized in that said core is coated with said first polymer, said polymer being particulate.

19. Process according to Claim 1, characterized in that the first polymer is poly(N-isopropylacrylamide) and the complexing groups are derived from itaconic acid or from maleic anhydride-co-methyl vinyl ether.

20. Process according to Claim 3 or according to the combination of Claims 3 and 19, characterized in that the second polymer is poly(N-isopropylacrylamide) and the complexing groups are derived from itaconic acid or from maleic anhydride-co-methyl vinyl ether.

21. Process according to Claim 1, characterized in that the first transition metal is chosen from zinc, nickel, copper, cobalt, iron, magnesium, manganese, lead, palladium, platinum and gold.

22. Process according to Claim 3 or according to the combination of Claims 3 and 21, characterized in that the second transition metal is chosen from zinc, nickel, copper, cobalt, iron, magnesium, manganese, lead, palladium, platinum and gold.

23. Process according to Claim 1, characterized in that the placing in contact of the first biological species with the capture phase is carried out at a pH above or equal to the isoelectric point of said first biological species.

24. Process according to Claim 3 or according to the combination of Claims 3 and 23, characterized in that the placing in contact of the second biological species with the detection phase is carried out at a pH above or equal to the isoelectric point of said second biological species.

25. Process according to Claim 1, characterized in that the first biological species is rich in histidine and/or cysteine.

26. Process according to Claim 3 or according to the combination of Claims 3 and 25, characterized in that the second biological species is rich in histidine and/or in cysteine.

27. Process according to Claim 1, characterized in that an agglutination reaction is used.

28. Process according to Claim 2 or 3, characterized in that the marker for the detection phase is chosen from the group consisting of an enzyme, biotin, iminobiotin, a fluorescent component, a

radioactive component, a chemiluminescent component, an electron-density component, a magnetic component, an antigen, a hapten and an antibody.

29. Process according to Claim 2 or 3, characterized in that the ELISA technique is used.

30. Use of a first particulate or linear polymer, of hydrophilic apparent nature, and first complexing groups, these groups being linked by coordination to a first transition metal, which is itself linked to a first biological species capable of recognizing the target biological material, as a phase for capturing a target biological material, in microparticulate or linear form.

31. Use of a second particulate or linear polymer, of hydrophilic apparent nature, and second complexing groups, these groups being linked by coordination to a second transition metal, which is itself linked to a second biological species capable of recognizing the target biological material, and a marker, as a phase for detecting a target biological material, in microparticulate or linear form.

32. Use of a first polymer according to Claim 30 and/or use of a second polymer according to Claim 31, in a reagent for isolating a target biological material.

09/403085

For receiving Office use only

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.
International Filing Date
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* MD/B05B2628

Box No. I TITLE OF INVENTION

PROCESS FOR ISOLATING A TARGET BIOLOGICAL MATERIAL, CAPTURE PHASE, DETECTION PHASE AND REAGENT

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BIO MERIEUX
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☐ This person is also inventor.

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State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ELAISSARI Abdelhamid
7 rue Jacques Monod
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This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
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This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
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This person is:
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☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
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69100 VILLEURBANNE

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
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29 rue du Parc
38180 SEYSSINS

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **CA** Canada
- ☒ **CH** and **LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic .....
- ☒ **DE** Germany .....
- ☒ **DK** Denmark .....
- ☒ **EE** Estonia .....
- ☒ **ES** Spain .....
- ☒ **FI** Finland .....
- ☒ **GB** United Kingdom
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia .....
- ☒ **HR** Croatia
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia
- ☒ **IL** Israel .....
- ☒ **IS** Iceland
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of Moldova .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian Federation .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia .....
- ☒ **SK** Slovakia .....
- ☒ **SL** Sierra Leone
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and Tobago .....
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except the designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (*day/month/year*)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 16 April 1997	97 04923	FRANCE		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (*only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office*) identified above as item(s): 1 97 04923

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / EP

Request to use results of earlier search: reference to that search (*if an earlier search has been carried out by or requested from the International Searching Authority*):

Date (*day/month/year*)	Number	Country (*or regional Office*)
30 January 1998	FA 545855	FRANCE

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:4
description (excluding sequence listing part)	:15
claims	:5
abstract	:1
drawings	:3
sequence listing part of description	:
Total number of sheets	:28

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (*specify*): 2 tax credit notes, 2 checks & search report

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

CABINET GERMAIN & MAUREAU
Mireille DIDIER
CPI 371202
Lyon, 16 April 1998

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

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Date of receipt of the record copy by the International Bureau: